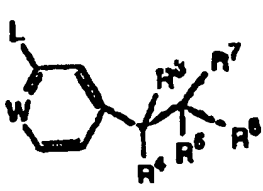




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07D 213/40, A61K 31/44, C07D 213/64, 213/74, 213/62, 311/60	A1	(11) International Publication Number: WO 97/23461 (43) International Publication Date: 3 July 1997 (03.07.97)
(21) International Application Number: PCT/GB96/03196 (22) International Filing Date: 20 December 1996 (20.12.96) (30) Priority Data: 9526245.7 21 December 1995 (21.12.95) GB (71) Applicant: CELLTECH THERAPEUTICS LIMITED [GB/GB]; 216 Bath Road, Slough, Berkshire SL1 4EN (GB). (72) Inventors: HEAD, John, Clifford; 4 Dorchester Close, Maidenhead, Berkshire SL6 6RX (GB). REUBERSON, James, Thomas; 46 Croft Hill Road, Slough, Berkshire SL2 1HF (GB). (74) Agent: SKAILES, Humphrey, John; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: TRI-SUBSTITUTED PHENYL DERIVATIVES USEFUL AS PDE IV INHIBITORS (57) Abstract <p>Compounds of general formula (1) are described, wherein W, L, R³, R⁴, R⁵, R⁶ and R⁷ have the meanings as defined in the description, according to which at least one of R⁴ or R⁵ is a -(CH₂)_nArN(R^b)CX¹N(R^b)L²(Alk)_mAr group. The compounds are phosphodiesterase type IV inhibitors and are useful in the prophylaxis and treatment of diseases such as asthma where an unwanted inflammatory response or muscular spasm is present.</p> <div style="text-align: right;">  <p>(1)</p> </div>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SG	Singapore
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LJ	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LR	Liberia	SZ	Swaziland
CS	Czechoslovakia	LT	Lithuania	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	LV	Latvia	TJ	Tajikistan
DK	Denmark	MC	Monaco	TT	Trinidad and Tobago
EE	Estonia	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	UG	Uganda
FI	Finland	ML	Mali	US	United States of America
FR	France	MN	Mongolia	UZ	Uzbekistan
GA	Gabon	MR	Mauritania	VN	Viet Nam

TRI-SUBSTITUTED PHENYL DERIVATIVES USEFUL AS
PDE IV INHIBITORS

- 5 This invention relates to a novel series of triarylethanes, to processes for their preparation, to pharmaceutical compositions containing them, and to their use in medicine.

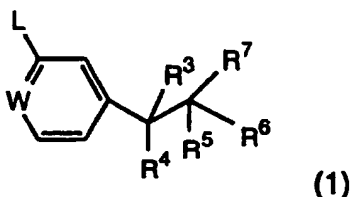
10 Many hormones and neurotransmitters modulate tissue function by elevating intra-cellular levels of adenosine 3', 5'-cyclic monophosphate (cAMP). The cellular levels of cAMP are regulated by mechanisms which control synthesis and breakdown. The synthesis of cAMP is controlled by adenylyl cyclase which may be directly activated by agents such as forskolin or indirectly activated by the binding of specific agonists to cell surface
15 receptors which are coupled to adenylyl cyclase. The breakdown of cAMP is controlled by a family of phosphodiesterase (PDE) isoenzymes, which also control the breakdown of guanosine 3',5'-cyclic monophosphate (cGMP). To date, seven members of the family have been described (PDE I-VII) the distribution of which varies from tissue to tissue. This
20 suggests that specific inhibitors of PDE isoenzymes could achieve differential elevation of cAMP in different tissues, [for reviews of PDE distribution, structure, function and regulation, see Beavo & Reifsnyder (1990) TIPS, 11: 150-155 and Nicholson et al (1991) TIPS, 12: 19-27].

- 25 There is clear evidence that elevation of cAMP in inflammatory leukocytes leads to inhibition of their activation. Furthermore, elevation of cAMP in airway smooth muscle has a spasmolytic effect. In these tissues, PDE IV plays a major role in the hydrolysis of cAMP. It can be expected, therefore, that selective inhibitors of PDE IV would have therapeutic
30 effects in inflammatory diseases such as asthma, by achieving both anti-inflammatory and bronchodilator effects.

35 In our International Patent Specification No. WO94/14742 we describe a series of triarylethanes which are potent inhibitors of the PDE IV isoenzyme at concentrations at which they have little or no inhibitory action on other PDE isoenzymes. The compounds are of use in medicine,

especially in the prophylaxis and treatment of asthma. An enantioselective process for the preparation of these compounds is described in our International Patent Specification No. WO95/17386.

- 5 We have now found a particular series of triarylethanes which are potent and selective PDE IV inhibitors and which also have other advantageous pharmacological properties, including especially good oral availability and improved metabolic stability.
- 10 Thus according to one aspect of the invention, we provide a compound of formula (1)



- 15 wherein
- =W- is (1) =C(Y)- where Y is a halogen atom, or an alkyl or -XR^a group where X is -O-, -S(O)_p- [where p is zero or an integer of value 1 or 2], or -N(R^b)- [where R^b is a hydrogen atom or an optionally substituted alkyl group] and R^a is a hydrogen atom or an optionally substituted alkyl group
- 20 or, (2) =N-;
- L is a -XR, [where R is an optionally substituted alkyl, alkenyl, cycloalkyl or cyloalkenyl group], -C(R¹¹)=C(R¹)(R²) or [-CH(R¹¹)]_nCH(R¹)(R²) group where R¹¹ is a hydrogen or a fluorine atom or a methyl group, and R¹ and R², which may be the same or different, is each a hydrogen or fluorine
- 25 atom or an optionally substituted alkyl, alkenyl, alkynyl, alkoxy, alkylthio, -CO₂R⁸, [where R⁸ is a hydrogen atom or an optionally substituted alkyl, aralkyl, or aryl group], -CONR⁹R¹⁰ [where R⁹ and R¹⁰, which may be the same or different is each as defined for R⁸], -CSNR⁹R¹⁰, -CN or -NO₂ group, or R¹ and R² together with the C atom to which they are attached
- 30 are linked to form an optionally substituted cycloalkyl or cycloalkenyl group and n is zero or the integer 1;
- R³ is a hydrogen or a fluorine atom, an optionally substituted straight or branched alkyl group, or a hydroxyl group;

- R⁴ is a hydrogen atom or group $-(CH_2)_tAr$ [where t is zero or an integer 1, 2 or 3 and Ar is a monocyclic or bicyclic aryl group, optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms] or a group $-(CH_2)_tAr-(L^1)_n-Ar'$ [where L¹ is a divalent linking group n is zero or an integer 1 and Ar' is -Ar, -CO(Alk)_mAr, [where Alk is an optionally substituted straight or branched C₁₋₆ alkylene, C₂₋₆ alkenylene or C₂₋₆ alkynylene chain optionally interrupted by one, two or three -O- or -S- atoms or -S(O)_q- (where q is an integer 1 or 2) or -N(R^b)- groups and m is zero or an integer 1], -SO₂(Alk)_nAr, -SO₂NH(Alk)_mAr, -SO₂N(Alk¹)(Alk)_mAr [where Alk¹ is as defined for Alk] -SO₂N[(Alk)_mAr]₂, -CONH(Alk)_mAr, -CON(Alk¹)(Alk)_mAr, -CON[(Alk)_mAr]₂, -N(Alk¹)SO₂(Alk)_mAr, -NHSO₂(Alk)_mAr, -N[SO₂(Alk)_mAr]₂, -NHSO₂NH(Alk)_mAr, -N(Alk¹)SO₂NH(Alk)_mAr, -NHSO₂N(Alk¹)(Alk)_mAr, -N(Alk¹)SO₂N(Alk¹)(Alk)_mAr, -NHSO₂N[(Alk)_mAr]₂, -N(Alk¹)SO₂N[(Alk)_mAr]₂, -NHC(O)(Alk)_mAr, -N(Alk¹)C(O)(Alk)_mAr, -N[C(O)(Alk)_mAr]₂, -NHC(O)NH(Alk)_mAr, -N(Alk¹)C(O)NH(Alk)_mAr, -NHC(O)N(Alk¹)(Alk)_mAr, -N(Alk¹)C(O)N(Alk¹)(Alk)_mAr, -NHC(O)O(Alk)_mAr, -N(Alk¹)C(O)O(Alk)_mAr, -C(S)NH(Alk)_mAr, -C(S)N(Alk¹)(Alk)_mAr, -C(S)N(Alk¹)(Alk)_mAr, -C(S)N[(Alk)_mAr]₂, -NHC(S)(Alk)_mAr, -N(Alk¹)C(S)(Alk)_mAr, -N[C(S)(Alk)_mAr]₂, -NHC(S)NH(Alk)_mAr, -N(Alk¹)C(S)NH(Alk)_mAr, -NHC(S)N(Alk¹)(Alk)_mAr, -N(Alk¹)C(S)N(Alk¹)(Alk)_mAr, -SO₂(Alk)_mNHet [where -NHet is an optionally substituted C₅₋₇ heterocyclic amino group optionally containing one or more other -O- or -S- atoms or -N(R^b)-, -C(O)- or -C(S)- groups], -CO(Alk)_mNHet, -CS(Alk)_mNHet, -NHSO₂(Alk)_mNHet, -NHC(O)(Alk)_mNHet, -NHC(S)(Alk)_mNHet, -SO₂NH((Alk)_mHet') [where Het' is an optionally substituted C₅₋₇ monocyclic carbocyclic group optionally containing one or more -O- or -S- atoms or -N(R^b)- groups], -CONH((Alk)_mHet'), -CSNH((Alk)_mHet'), -NHSO₂NH((Alk)_mHet'), -NHC(O)NH(Alk)_m(Het') or -NHC(S)NH(Alk)_m(Het') group] or R⁴ is a $-(CH_2)_tArN(R^b)CX^1N(R^b)L^2(Alk)_mAr$ group where X is an oxygen or sulphur atom and L² is a divalent linking group;
- R⁵ is a $-(CH_2)_tAr$, $-(CH_2)_tAr-(L^1)_n-Ar'$ or $-(CH_2)_tArN(R^b)CX^1N(R^b)L^2(Alk)_mAr$ group, provided that at least one of R⁴ or R⁵ is a $-(CH_2)_tArN(R^b)CX^1N(R^b)L^2(Alk)_mAr$ group;

R⁶ is a hydrogen or a fluorine atom, or an optionally substituted alkyl group;

R⁷ is a hydrogen or a fluorine atom, an optionally substituted straight or branched alkyl group or an OR^c group where R^c is a hydrogen atom or an optionally substituted alkyl or alkenyl group, or an alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group; and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

It will be appreciated that certain compounds of formula (1) may have one or more chiral centres, depending on the nature of the groups L, R¹, R², R³, R⁴, R⁵, R⁶ and R⁷. Where one or more chiral centres is present, enantiomers or diastereomers may exist, and the invention is to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates.

Compounds of formula (1) wherein L is a -C(R¹¹)=C(R¹)(R²) group may exist as geometric isomers depending on the nature of the groups R¹, R², and R¹¹ and the invention is to be understood to extend to all such isomers and mixtures thereof.

In the compounds of formula (1), when =W- is =C(Y)- and Y is a halogen atom Y may be for example a fluorine, chlorine, bromine or iodine atom.

When W in the compounds of formula (1) is a group =C(Y)- and Y is -XR^a, R^a may be, for example, a hydrogen atom or an optionally substituted straight or branched alkyl group, for example, an optionally substituted C₁₋₆alkyl group, such as a methyl, ethyl, n-propyl or i-propyl group. Optional substituents which may be present on R^a groups include one or more halogen atoms, e.g. fluorine, or chlorine atoms. Particular R^a groups include for example -CH₂F, -CH₂Cl, -CHF₂, -CHCl₂, -CF₃ or -CCl₃ groups.

When =W- in the compounds of formula (1) is a group =C(Y)- where -Y is -N(R^b), =W- may be a =C(NH₂)-, =C(NHCH₃)- or =C(NHC₂H₅)- group.

In compounds of formula (1), X may be an oxygen or a sulphur atom, or a group -S(O)-, -S(O)₂-, -NH- or C₁₋₆ alkylamino, for example a C₁₋₃ alkylamino, e.g. methylamino [-N(CH₃)-] or ethylamino [-N(C₂H₅)-] group.

- 5 Alkyl groups represented by Y, R, R¹, R², or R^b in the compounds of formula (1) include optionally substituted straight or branched C₁₋₆ alkyl groups optionally interrupted by one or more X atoms or groups. Particular examples include C₁₋₃ alkyl groups such as methyl or ethyl groups. Optional substituents on these groups include one, two or three
- 10 substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl or C₁₋₆ alkoxy e.g. C₁₋₃ alkoxy such as methoxy or ethoxy or -CO₂R⁸, -CONR⁹R¹⁰, -CSNR⁹R¹⁰ or -CN groups.

- Alkenyl groups represented by R, R¹ or R² in the compounds of formula
- 15 (1) include optionally substituted straight or branched C₂₋₆alkenyl groups optionally interrupted by one or more X atoms or groups. Particular examples include ethenyl, propen-1-yl and 2-methylpropen-1-yl groups. Optional substituents include those described above in relation to alkyl groups represented by the groups R¹ or R².

- 20 Alkynyl groups represented by R¹ or R² in compounds of formula (1) include optionally substituted straight or branched C₂₋₆alkynyl groups optionally interrupted by one or more X atoms or groups. Particular examples include ethynyl and propyn-1-yl groups. Optional substituents
- 25 include those described above in relation to alkyl groups represented by the groups R¹ or R².

- When R¹ or R² in compounds of formula (1) is an alkoxy or alkylthio group it may be for example an optionally substituted straight or branched C₁₋₆
- 30 alkoxy or C₁₋₆alkylthio group optionally interrupted by one or more X atoms or groups. Particular examples include C₁₋₃alkoxy, e.g. methoxy or ethoxy, or C₁₋₃alkylthio e.g. methylthio or ethylthio groups. Optional substituents include those described above in relation to alkyl groups represented by the groups R¹ or R².

When R¹ and R² together with the carbon atom to which they are attached in the compounds of formula (1) are linked to form a cycloalkyl or cycloalkenyl group, the group may be for example a C₃₋₈cycloalkyl group such as a cyclobutyl, cyclopentyl or cyclohexyl group or a C₃₋₈ cycloalkenyl group containing for example one or two double bonds such as a 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 2,4-cyclohexadien-1-yl or 3,5-cyclohexadien-1-yl group, each cycloalkyl or cycloalkenyl group being optionally substituted by one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, straight or branched C₁₋₆alkyl e.g. C₁₋₃alkyl such as methyl or ethyl, hydroxyl or C₁₋₆alkoxy e.g. C₁₋₃alkoxy such as methoxy or ethoxy groups.

When R in the compounds of formula (1) is an optionally substituted cycloalkyl or cycloalkenyl group it may be for example a C₃₋₈cycloalkyl group such as a cyclobutyl, cyclopentyl or cyclohexyl group or a C₃₋₈cycloalkenyl group containing for example one or two double bonds such as a 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 2,4-cyclohexadien-1-yl or 3,5-cyclohexadien-1-yl group, each cycloalkyl or cycloalkenyl group being optionally substituted by one, two or three substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, straight or branched C₁₋₆alkyl e.g. C₁₋₃alkyl such as methyl or ethyl, hydroxyl or C₁₋₆alkoxy e.g. C₁₋₃alkoxy such as methoxy or ethoxy groups.

When the group R⁷ in compounds of formula (1) is an OR^c group it may be for example a hydroxyl group; or a group -OR^c where R^c is an optionally substituted straight or branched C₁₋₆alkyl group, e.g. a C₁₋₃alkyl group such as a methyl or ethyl group, a C₂₋₆alkenyl group such as an ethenyl or 2-propen-1-yl group, a C₁₋₃alkoxyC₁₋₃alkyl group such as a methoxymethyl, ethoxymethyl or ethoxyethyl group, a C₁₋₆alkanoyl, e.g. C₁₋₃alkanoyl group such as an acetyl group, or a formyl [HC(O)-], carboxamido (CONR¹²R^{12a}) or thiocarboxamido (CSNR¹²R^{12a}) group, where R¹² and R^{12a} in each instance may be the same or different and is each a hydrogen atom or an optionally substituted straight or branched C₁₋

alkyl, e.g. C₁₋₃alkyl group such as methyl or ethyl group. Optional substituents which may be present on such R^c, R¹² or R^{12a} groups include those described below in relation to the alkyl groups R⁶ or R⁷.

- 5 Alkyl groups represented by R³, R⁶ or R⁷ in compounds of formula (1) include optionally substituted straight or branched C₁₋₆ alkyl groups, e.g. C₁₋₃ alkyl groups such as methyl, ethyl, n-propyl or i-propyl groups. Optional substituents which may be present on these groups include one or more halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or
- 10 hydroxyl or C₁₋₆alkoxy e.g. C₁₋₃alkoxy such as methoxy or ethoxy groups.

When the group R⁶ in compounds of formula (1) is a halogen atom it may be for example a fluorine, chlorine, bromine or iodine atom.

- 15 When R¹ or R² is a -CO₂R⁸, -CONR⁹R¹⁰ or CSNR⁹R¹⁰ group or these groups appear as substituents, the groups may be for example a -CO₂H, -CONH₂ or -CSNH₂ group or a group -CO₂R⁸, -CONR⁹R¹⁰, -CSNR⁹R¹⁰, -CONHR¹⁰, or -CSNHR¹⁰ where R⁸, R⁹ and R¹⁰ where present is a C₁₋₃alkyl group such as methyl or ethyl group, a C₆₋₁₂aryl group, for example
- 20 an optionally substituted phenyl, or a 1- or 2- naphthyl group, or a C₆₋₁₂aryl C₁₋₃alkyl group such as an optionally substituted benzyl or phenethyl group. Optional substituents which may be present on these aryl groups include R¹³ substituents discussed below in relation to the group Ar.

25

In the compounds of formula (1), the groups -(CH₂)_tAr and -(CH₂)_tAr(L¹)_nAr' when present may be -Ar, -CH₂Ar, -(CH₂)₂Ar, -(CH₂)₃Ar, -Ar-Ar', -Ar-L¹-Ar', -CH₂ArAr', -CH₂ArL¹Ar', -(CH₂)₂ArAr', -(CH₂)₂ArL¹Ar', -(CH₂)₃ArAr' or -(CH₂)₃ArL¹Ar' groups.

30

Monocyclic or bicyclic aryl groups represented by the group Ar or Ar' in compounds of formula (1) include for example C₆₋₁₂ optionally substituted aryl groups, for example optionally substituted phenyl, 1-or 2-naphthyl, indenyl or isoindenyl groups.

35

When the monocyclic or bicyclic aryl group Ar or Ar' contains one or more heteroatoms, Ar or Ar' may be for example a C₁₋₉ optionally substituted heteroaryl group containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general,
5 Ar or Ar' heteroaryl groups may be for example monocyclic or bicyclic heteroaryl groups. Monocyclic heteroaryl groups include for example five- or six-membered heteroaryl groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaryl groups include for example nine- or ten- membered heteroaryl
10 groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Examples of heteroaryl groups represented by Ar or Ar' include pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethylimidazolyl, oxazolyl,
15 isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, isobenzofuryl, benzothienyl, isobenzothienyl, indolyl, isoindolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl,
20 quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl. Example of bicyclic heteroaryl groups include quinolinyl or isoquinolinyl groups.

25 The heteroaryl group represented by Ar or Ar' may be attached to the remainder of the molecule of formula (1) through any ring carbon or heteroatom as appropriate. Thus, for example, when the group Ar or Ar' is a pyridyl group it may be a 2-pyridyl, 3-pyridyl or 4-pyridyl group. When it is a thienyl group it may be a 2-thienyl or 3-thienyl group; and, similarly,
30 when it is a furyl group it may be a 2-furyl or 3-furyl group. In another example, when the group Ar or Ar' is a quinolinyl group it may be a 2-, 3-, 4-, 5-, 6-, 7- or 8- quinolinyl and when it is an isoquinolinyl, it may be a 1-, 3-, 4-, 5-, 6-, 7- or 8- isoquinolinyl group.

35 When in compounds of formula (1) the Ar or Ar' group is a nitrogen-containing heterocycle it may be possible to form quaternary salts, for

example N-alkyl quaternary salts and the invention is to be understood to extend to such salts. Thus for example when the group Ar or Ar' is a pyridyl group, pyridinium salts may be formed, for example N-alkylpyridinium salts such as N-methylpyridinium.

5

The aryl or heteroaryl groups represented by Ar or Ar' in compounds of formula (1) may each optionally be substituted by one, two, three or more substituents [R¹³]. The substituent R¹³ may be selected from an atom or group R¹⁴ or -Alk²(R¹⁴)_m wherein R¹⁴ is a halogen atom, or an amino
 10 (-NH₂), substituted amino, nitro, cyano, hydroxyl (-OH), substituted hydroxyl, cycloalkoxy, formyl [HC(O)-], carboxyl (-CO₂H), esterified carboxyl, thiol (-SH), substituted thiol, -C(O)Alk², -SO₃H, -SO₂Alk², -SO₂NH₂, -SO₂NHAlk², -SO₂N[Alk²]₂, -CONH₂, -CONHAlk², -CON[Alk²]₂, -NHSO₂H, -NAlk²SO₂H, -NHSO₂Alk², -NAlk²SO₂Alk², -N[SO₂Alk²]₂,
 15 -NHSO₂NH₂, -NAlk²SO₂NH₂, -NHSO₂NHAlk², -NAlk²SO₂NHAlk², -NHSO₂N[Alk²]₂, -NAlk²SO₂N[Alk²]₂, -NHC(O)H, -NHC(O)Alk², -NAlk²C(O)H, -NAlk²C(O)Alk², -N[C(O)Alk²]₂, -NHC(O)OH, -NHC(O)OAlk², -NAlk²C(O)OH, -NAlk²C(O)OAlk², -NHCONH₂, -NHCONHAlk², -NHCON[Alk²]₂, -NAlk²CON[Alk²]₂, -NAlk²CONH[Alk²]₂,
 20 -NAlk²CONH₂, -C(S)H, -C(S)Alk², -CSNH₂, -CSNHAlk², -CSN[Alk²]₂, -NHC(S)H, -NHCSAlk², -NAlk²C(S)H, -NAlk²C(S)Alk², -N[C(S)Alk²]₂, -N[C(O)Alk²]SO₂H, -NHCSNH₂, -NHCSNHAlk², -NHCSN[Alk²]₂, -NAlk²CSN[Alk²]₂, -NAlk²CSNHAlk², -NAlk²CSNH₂, or -N[C(O)Alk²]SO₂Alk² group, Alk² is a straight or branched C₁₋₆ alkylene, C₂₋₆alkenylene, or C₂₋₆alkynylene chain optionally interrupted by one, two,
 25 or three -O-, or -S- atoms or -S(O)_p-, [where p is an integer 1 or 2] or -N(R⁸)- groups; and m is zero or an integer 1, 2 or 3.

When in the group -Alk²(R¹⁴)_m m is an integer 1, 2 or 3, it is to be
 30 understood that the substituent or substituents R¹⁴ may be present on any suitable carbon atom in -Alk². Where more than one R¹⁴ substituent is present these may be the same or different and may be present on the same or different carbon atom in Alk². Clearly, when m is zero and no substituent R¹⁴ is present or when Alk² forms part of a group such as
 35 -SO₂Alk² the alkylene, alkenylene or alkynylene chain represented by Alk² becomes an alkyl, alkenyl or alkynyl group.

When R^{14} is a substituted amino group it may be a group $-NH[Alk^2(R^{14a})_m]$ [where Alk^2 and m are as defined above and R^{14a} is as defined above for R^{14} but is not a substituted amino, a substituted hydroxyl or a substituted thiol group] or a group $-N[Alk^2(R^{14a})_m]_2$ wherein each $-Alk^2(R^{14a})_m$ group is the same or different.

When R^{14} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

10

When R^{14} is a cycloalkoxy group it may be for example a C_{5-7} cycloalkoxy group such as a cyclopentyloxy or cyclohexyloxy group.

When R^{14} is a substituted hydroxyl or substituted thiol group it may be a group $-OAlk^2(R^{14a})_m$ or $-SAlk^2(R^{14a})_m$ respectively, where Alk^2 , R^{14a} and m are as just defined.

Esterified carboxyl groups represented by the group R^{14} include groups of formula $-CO_2Alk^3$ wherein Alk^3 is a straight or branched, optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12} aryl C_{1-8} alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12} aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12} aryloxy C_{1-8} alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted C_{1-8} alkanoyloxy C_{1-8} alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12} aroyloxy C_{1-8} alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^3 group include R^{13} substituents described above.

It will be appreciated that the group Ar or Ar' may be attached to the remainder of the molecule of formula (1) through either a ring carbon atom or heteroatom.

35

Particular examples of the chain Alk^2 when present include methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butylnylene or 3-butylnylene chain, optionally
 5 interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)₂- or -N(R^b)- groups.

Particularly useful atoms or groups represented by R¹³ include fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl or ethyl,
 10 C₁₋₆alkylamino, e.g. methylamino or ethylamino, C₁₋₆ hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, C₁₋₆alkylthiol e.g. methylthiol or ethylthiol, C₁₋₆alkoxy, e.g. methoxy or ethoxy, C₅₋₇cycloalkoxy, e.g. cyclopentyloxy, haloC₁₋₆alkyl, e.g. trifluoromethyl, C₁₋₆alkylamino, e.g. methylamino or ethylamino, amino (-NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl,
 15 C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂Alk³ [where Alk³ is as defined above], C₁₋₆alkanoyl e.g. acetyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, sulphonyl (-SO₃H), C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl,
 20 e.g. methylaminosulphonyl or ethylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, sulphonylamino (-NHSO₂H),
 25 C₁₋₆alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino (-NHSO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, C₁₋₆alkanoylamino, e.g. acetilamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g. acetilaminomethyl or C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino thiocarboxamido (-CSNH₂), C₁₋₆alkylaminothiocarbonyl, e.g. methylaminothiocarbonyl or ethylaminothiocarbonyl,
 30 C₁₋₆dialkylaminothiocarbonyl, e.g. dimethylaminothiocarbonyl or diethylaminothiocarbonyl, aminocarbonylamino, C₁₋₆alkylaminocarbonylamino,

e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, aminothiocabonylamino, C₁₋₆alkylaminothiocabonylamino, e.g. methylaminothiocabonylamino or ethylaminothiocabonylamino, C₁₋₆ dialkylaminothiocabonylamino, e.g. dimethylaminothiocabonylamino, or diethylaminothiocabonylamino, aminocarbonylC₁₋₆alkylamino, e.g. aminocarbonylmethylamino or aminocarbonylethylamino, aminothiocabonylC₁₋₆alkylamino e.g. aminothiocabonylmethylamino or aminothiocabonylethylamino, formylaminoC₁₋₆ alkylsulphonylamino, e.g. formylaminomethylsulphonylamino or formyl-aminoethylsulphonylamino, thioformylaminoC₁₋₆alkylsulphonylamino, e.g. thioformylaminomethylsulphonylamino or thioformylethylsulphonylamino, C₁₋₆acylaminosulphonylamino, e.g. acetylaminosulphonylamino, C₁₋₆thio-acylaminosulphonylamino, e.g. thioacetylaminosulphonylamino groups.

15

Where desired, two R¹³ substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C₂₋₆alkylenedioxy group such as ethylenedioxy.

20 It will be appreciated that where two or more R¹³ substituents are present, these need not necessarily be the same atoms and/or groups. The R¹³ substituents may be present at any ring carbon atom away from that attached to the rest of the molecule of formula (1). Thus, for example, in phenyl groups represented by Ar or Ar' any substituent may be present at
25 the 2-, 3-, 4-, 5- or 6- positions relative to the ring carbon atom attached to the remainder of the molecule.

In the compounds of formula (1), when the group -(CH₂)_tAr(L¹)_nAr' is present in R⁴ and/or R⁵, the linker group L¹ may be any divalent linking
30 group. Particular examples of L¹ groups which may be present in compounds of the invention include groups of formula -(Alk⁴)_r(X^a)_s(Alk⁵)_t where Alk⁴ and Alk⁵ is each an optionally substituted straight or branched C₁₋₆alkylene, C₂₋₆alkenylene or C₂₋₆alkynylene chain optionally interrupted by one or more, e.g. one, two or three heteroatoms or carbocyclic or
35 heteroatom-containing groups, X^a is an -O- or -S- atom or a -S(O)-, -S(O)₂- or -N(R^b)- group, r is zero or the integer 1, t is zero or the integer 1 and s is

zero or the integer 1, provided that when one of r , s , or t is zero at least one of the remainder is the integer 1.

The heteroatoms which may interrupt the Alk^4 or Alk^5 chains include for example -O- or -S- atoms. Carbocyclic groups include for example cycloalkyl, e.g. cyclopentyl or cyclohexyl, or cycloalkenyl e.g. cyclopentenyl or cyclohexenyl, groups. Particular heteroatom-containing groups which may interrupt Alk^4 or Alk^5 include oxygen-, sulphur- or nitrogen-containing groups such as -S(O)-, -S(O)₂-, -N(R^b)-, -C(O)-, -C(S)-, -C(NR^b)-, -CON(R^b)-, -CSN(R^b)-, -N(R^b)CO-, -N(R^b)CS-, -SON(R^b)-, -SO₂N(R^b)-, -N(R^b)SO-, -N(R^b)SO₂-, -N(R^b)SO₂N(R^b)-, -N(R^b)SON(R^b)-, or -N(R^b)CON(R^b)- groups. It will be appreciated that when the chains Alk^4 or Alk^5 are interrupted by two or more heteroatoms, carbocyclic or heteroatom-containing groups, such atoms or groups may be adjacent to one another, for example to form a group -N(R^b)-C(NR^b)-N(R^b)- or -O-CONH-.

Optional substituents which may be present on Alk^4 or Alk^5 chains include those described above in relation to the group R¹ when it is an alkyl group.

The group $-(\text{L}^1)_n\text{Ar}'$ may be attached to the group Ar through any available carbon or heteroatoms present in the two groups. Thus, for example, when Ar is a phenyl group, $-(\text{L}^1)_n\text{Ar}'$ may be attached through a carbon or heteroatom in $-(\text{L}^1)_n\text{Ar}'$ to a carbon atom in Ar at the 2-, 3-, 4-, 5-, or 6-position relative to the Ar carbon atom attached to the remainder of the molecule.

In the group $(\text{L}^1)_n\text{Ar}'$ particular examples of Alk^4 or Alk^5 include optionally substituted methylene, ethylene, propylene, butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butyneylene or 3-butyneylene chains, optionally interrupted by one, two or three heteroatoms, carbocyclic or heteroatom-containing groups as described above.

Particular examples of the group $-(\text{L}^1)_n\text{Ar}'$ include the groups $-\text{Alk}^4\text{Ar}'$, $-\text{XAr}'$, $-\text{Alk}^4\text{XAr}'$ and $-\text{XAlk}^5\text{Ar}'$, especially for example $-\text{CH}_2\text{Ar}'$, $-(\text{CH}_2)_2\text{Ar}'$,

-(CH₂)₃Ar', -CH₂OCH₂Ar', -CH₂SCH₂Ar', -CH₂N(R^b)CH₂Ar', -CH=CHAr',
 -CH₂CH=CHAr', -OAr', -SAr', -N(R^b)Ar', -CH₂OAr', -CH₂SAr',
 -CH₂N(R^b)Ar', -CH₂OCH₂OAr', -OCH₂Ar', -O(CH₂)₂Ar', -SCH₂Ar',
 -S(CH₂)₂Ar', -N(R^b)CH₂Ar' and -N(R^b)(CH₂)₂Ar'. In these particular
 5 groups, Ar' may be as generally described herein and as particularly
 described below.

In general, and in the particular groups just mentioned, Alk in Ar' may be an
 optionally substituted methylene, ethylene, n-propylene, i-propylene, n-
 10 butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene,
 3-butenylene, ethynylene, 2-propenylene, 2-butyneylene, or 3-butyneylene
 chain optionally interrupted by one, two or three -O- or -S- atoms or -S(O)-,
 -S(O)₂- or -N(R^b)- groups. Optional substituents which may be present
 15 include one or more halogen atoms, e.g. fluorine, chlorine, bromine or
 iodine atoms, or hydroxyl or C₁₋₆alkoxy e.g. C₁₋₃alkoxy such as methoxy or
 ethoxy groups. The group Alk¹ when present in Ar' may also be as just
 described for Alk, but will clearly be an alkyl, alkenyl or alkynyl group,
 rather than a corresponding alkylene, alkenylene or alkynylene chain.

20 Particular examples of the group Ar' include optionally substituted C₆₋₁₂aryl
 or C₁₋₉heteroaryl groups, especially optionally substituted phenyl or pyridyl
 groups, or, in particular, -CO(Alk)_mPh (where Ph is an optionally
 substituted phenyl group), -SONH(Alk)_mPh, -SO₂N(Alk¹)(Alk)_mPh,
 -SO₂N[(Alk)_mPh]₂, -CONH(Alk)_mPh, -CON(Alk¹)(Alk)_mPh,
 25 -CON[(Alk)_mPh]₂, -NAlk¹SO₂(Alk)_mPh, -NH₂SO₂N(Alk¹)(Alk)_mPh,
 -NAlk¹SO₂Alk¹(Alk)_mPh, -NH₂SO₂N[(Alk)_mPh]₂, -NAlk¹SO₂N[(Alk)_mPh]₂,
 -NHC(O)(Alk)_mPh, -NAlk¹CO(Alk)_mPh, -NC(O)N[(Alk)_mPh]₂,
 -NHC(O)NH(Alk)_mPh, -NAlk¹C(O)NH(Alk)_mPh,
 -NHC(O)N(Alk¹)(Alk)_mPh, -NAlk¹C(O)N(Alk¹)(Alk)_mPh,
 30 -NHC(O)O(Alk)_mPh, -NAlk¹C(O)O(Alk)_mPh, -C(S)NH(Alk)_mPh,
 -C(S)N(Alk¹)(Alk)_mPh, -N(S)N[(Alk)_mPh]₂, -NHC(S)(Alk)_mPh,
 -N(Alk¹)C(S)(Alk)_mPh, -N[C(S)(Alk)_mPh]₂, -NHC(S)NH(Alk)_mPh,
 -NAlk¹C(S)NH(Alk)_mPh, -NHC(S)N(Alk¹)(Alk)_mPh, or
 -N(Alk¹)C(S)N(Alk¹)(Alk)_mPh groups. In these groups, the groups Alk and
 35 Alk¹ may in particular each be a methylene or ethylene, and a methyl or
 ethyl group respectively and m may be zero or in particular 1.

When in R⁴ and/or R⁵ a -NHet group is present this may be for example a pyrrolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, piperazinyl or thiomorpholinyl group. Optional substituents that may be present in such groups
5 include R¹³ substituents described above in relation to Ar or Ar' groups.

When in R⁴ and/or R⁵ a Het' group is present this may be for example a pyrrolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl, cyclopentyl, or cyclohexyl group. Optional substituents that
10 may be present on such groups include R¹³ substituents described above.

In the compounds of formula (1), when an ester group is present, for example a group CO₂R⁸ or -CO₂Alk³ this may advantageously be a metabolically labile ester.

15

In the -(CH₂)_tArN(R^b)CX¹N(R^b)L²(Alk)_mAr group present as R⁴ and/or R⁵ in compounds of formula (1) the divalent linking group represented by L² may be for example a -S(O)-, -S(O)N(R^b)-, -S(O)₂-, -S(O)₂N(R^b)-, -C(O)-, -C(O)N(R^b)-, -C(S)- or -C(S)N(R)- group. All the other groups represented
20 by -(CH₂)_t, Ar, R^b, X¹, and (Alk)_m may be as generally and particularly discussed above.

Particular examples of R⁴ and/or R⁵ groups of these types include -ArN(R^b)CONHSO₂(Alk)_mAr and -ArN(R^b)CONHSO₂N(R²)(Alk)_mAr
25 groups, especially where Ar is an optionally substituted phenyl group.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived
30 from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isethionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or
35 napsylates, phosphates, sulphates, hydrogen sulphates, acetates,

trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

5 Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

10 Prodrugs of compounds of formula (1) include those compounds, for example esters, alcohols or aminos, which are convertible *in vivo* by metabolic means, e.g. by hydrolysis, reduction, oxidation or transesterification, to compounds of formula (1).

15 Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

20 In the compounds of formula (1) the group =W- is preferably a =C(Y)-group. In compounds of this type Y is preferably a -XR^a group where X is -O- and R^a is an optionally substituted ethyl group or, especially, an optionally substituted methyl group. Especially useful substituents which may be present on R^a groups include one, two or three fluorine or chlorine atoms.

25 One particularly useful group of compounds of the invention has the formula (1) where L is a group -XR. In compounds of this type X is preferably -O-. The group R in these compounds is preferably an optionally substituted cycloalkyl group, particularly an optionally substituted cyclopentyl group, and is, especially a cyclopentyl group.

30 In another group of compounds of formula (1) L is preferably a -CH=C(R¹)(R²) group. In compounds of this type R¹ and R² are preferably linked together with the C atom to which they are attached to form an optionally substituted cycloalkyl or cycloalkenyl group, especially a substituted cyclopentyl or cyclohexyl or, especially, a cyclopentyl or cyclohexyl group.

35

The groups R^4 and R^5 in compounds of formula (1) is each, independently, preferably a CH_2Ar , $-CH_2Ar(L^1)_nAr'$ or $-CH_2ArN(R^b)CX^1N(R^b)L^2(Alk)_mAr$ group or especially an $-Ar$, $Ar-Ar'$, ArL^1Ar' or $-ArN(R^b)CX^1N(R^b)L^2(Alk)_mAr$ group, with the proviso mentioned in connection with formula (1). In one preference the group R^4 is especially a $-ArN(R^b)CX^1N(R^b)L^2(Alk)_mAr$ group and R^5 is an $-Ar$ group. Particularly useful R^4 or R^5 groups of these types include those groups in which Ar or Ar' is a monocyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur, or, in particular, nitrogen atoms, and optionally substituted by one, two, three or more R^{13} substituents. In these compounds, when the group represented by Ar or Ar' is a heteroaryl group it is preferably a nitrogen-containing monocyclic heteroaryl group, especially a six-membered nitrogen-containing heteroaryl group. Thus, in one preferred example, the groups R^4 and R^5 may each contain a six-membered nitrogen-containing heteroaryl Ar or Ar' group. In another preferred example R^4 may contain a monocyclic aryl group or a monocyclic or bicyclic heteroaryl group Ar or Ar' containing one or more oxygen, sulphur or nitrogen atoms and R^5 may contain a six-membered nitrogen-containing heteroaryl group Ar or Ar' . In these examples, the six-membered nitrogen-containing heteroaryl group may be an optionally substituted pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or imidazolyl group. Particular examples include optionally substituted 2-pyridyl, 3-pyridyl, 5-imidazolyl, or, especially, 4-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl or 3-pyrazinyl. The monocyclic aryl group may be a phenyl group or a substituted phenyl group, and the monocyclic or bicyclic heteroaryl group containing one or more oxygen, sulphur or nitrogen atom may be an optionally substituted 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-thiazolyl, 2-benzo(b)thiophenyl, 2-benzo(b)furyl or 4-isoquinolinyl group.

In another preference relating to R^4 groups of the just mentioned particular types, Ar' is a $-NHC(O)NH(Alk)_mPh$ (where Ph is as just described, $-NHCH_3C(O)NH(Alk)_mPh$, $-NHC(O)N(CH_3)(Alk)_mPh$, $-N(CH_3)C(O)N(CH_3)(Alk)_mPh$, $-CO(Alk)_mPh$, $-NHSO_2NH(Alk)_mPh$, $-N(CH_3)SO_2NH(Alk)_mPh$, $-N(CH_3)SO_2N(CH_3)(Alk)_mPh$, $-NHCO(Alk)_mPh$, $-N(CH_3)CO(Alk)_mPh$ or $-NHSO_2(Alk)_mPh$ group.

In general in compounds of formula (1) when R⁴ and/or R⁵ contains a substituted phenyl group it may be for example a mono-, di- or trisubstituted phenyl group in which the substituent is an atom or group
5 R¹³ as defined above. When the R⁴ and/or R⁵ group contains a monosubstituted phenyl group the substituent may be in the 2-, or preferably 3-, or especially 4-position relative to the ring carbon atom attached to the remainder of the molecule. When the R⁴ and/or R⁵ group contains a disubstituted phenyl group, the substituents may be in the 2,6
10 position relative to the ring carbon atom attached to the remainder of the molecule.

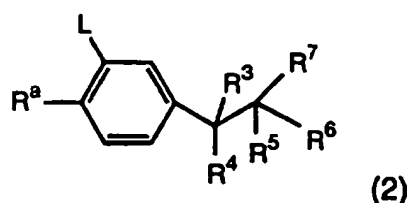
Particularly useful substituents R¹³ which may be present on Ar groups in R⁴ and R⁵, especially on phenyl groups, include halogen atoms or alkyl,
15 haloalkyl, amino, substituted amino, nitro, -NHSO₂NH₂, -NHSO₂NHCH₃, -NHSO₂N(CH₃)₂, -NHCOCH₃, -NHC(O)NH₂, -NCH₃C(O)NH₂, -NHC(O)NHCH₃, -NHC(O)NHCH₂CH₃, or -NHC(O)N(CH₃)₂ groups, each of said atoms or groups being optionally separated from the remainder of the Ar group by a group Alk² as defined above.

20

When in compounds of formula (1) R⁴ and/or R⁵ contains a substituted pyridyl group it may be for example a mono- or disubstituted pyridyl group, such as a mono- or disubstituted 2-pyridyl, 3-pyridyl or especially 4-pyridyl group substituted by one or two atoms or groups R¹³ as defined above, in
25 particular one or two halogen atoms such as fluorine or chlorine atoms, or methyl, methoxy, hydroxyl or nitro groups. Particularly useful pyridyl groups of these types are 3-monosubstituted-4-pyridyl or 3,5-disubstituted-4-pyridyl, or 2- or 4-monosubstituted-3-pyridyl or 2,4-disubstituted-3-pyridyl groups.

30

A particularly useful group of compounds of formula (1) has the formula (2):



where -L is a OR, where R is an optionally substituted cycloalkyl group, -CH=C(R¹)(R²) or -CH₂CH(R¹)(R²) group where R¹ and R² are linked together with the carbon atom to which they are attached to form a cycloalkyl group; R^a is an optionally substituted alkyl group and R³, R⁴, R⁵, R⁶ and R⁷ are as defined for formula (1); and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

In the compounds of formulae (1) or (2) one preferred group of compounds are those where the group R³ is a hydrogen atom; the group R⁶ is a methyl group, or especially a hydrogen atom; the group R⁷ is a methyl group, or especially a hydrogen atom; and R⁴ and R⁵ are as defined for formula (1). In compounds of this type R⁶ and R⁷ is each especially a hydrogen atom.

In general in compounds of formulae (1) or (2) R³, R⁶ and R⁷ is each especially a hydrogen atom, R⁵ is in particular a -(CH₂)_tAr group, especially an optionally substituted pyridyl group, especially a 4-pyridyl group. The group R⁴ in compounds of these types is preferably an -ArN(R^b)CX¹N(R^b)L²(Alk)_mAr group, particularly where each Ar group is a monocyclic aryl group optionally containing one or more heteroatoms selected from oxygen, sulphur or, especially, nitrogen atoms. Particularly useful R⁴ groups are those of formula -ArN(R^b)CX¹N(R^b)S(O)₂(Alk)_mAr or -ArN(R^b)CX¹N(R^b)S(O)₂N(R^b)(Alk)_mAr, especially where each Ar group is an optionally substituted phenyl group. Particular examples of such groups include -ArNHCONHS(O)₂Ar, -ArNHCSNHS(O)₂Ar, -ArNHCONHS(O)₂NHAr and -ArNHCSNHS(O)₂NHAr, especially where in each instance Ar is an optionally substituted phenyl group as defined herein. In general in these compounds, when Ar is a phenyl group the -N(R^b)CX¹N(R^b)L²(Alk)_mAr group is preferably attached to this group at

the 3- or 4-position of the phenyl ring relative to the point of attachment of the ring to the remainder of the molecule of formula (1).

In one particular group of compounds of formulae (1) or (2) R⁴ is preferably a -ArNHCONHS(O)₂Ar' group wherein Ar is a phenyl group and Ar' is an optionally substituted phenyl group. In these compounds the -NHCONHS(O)₂Ar' group is preferably attached to the Ar group at the 3- or 4-position of the phenyl ring as explained above. In this particular group of compounds the other groups W, L, R³, R⁵, R⁶ and R⁷ may be as generally or particularly defined above.

Particularly useful compounds according to the invention are:

(R)-N-[4-{1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethyl}phenyl]-N'-(phenylsulphonyl) urea;
(R)-N-[4-{1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethyl}phenyl]-N'-(methylphenylsulphonyl) urea; and
(R)-N-[4-{1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethyl}phenyl]-N'-(4-chlorophenylsulphonyl) urea;
and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

20

Compounds according to the invention are selective and potent inhibitors of PDE IV and advantageously have improved metabolic stability. The ability of the compounds to act in this way may be simply determined by the tests described in the Examples hereinafter.

25

Particular uses to which the compounds of the invention may be put include the prophylaxis and treatment of asthma, especially inflamed lung associated with asthma, cystic fibrosis, or in the treatment of inflammatory airway disease, chronic bronchitis, eosinophilic granuloma, psoriasis and other benign and malignant proliferative skin diseases, endotoxic shock, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis and arteriosclerosis.

35

Compounds of the invention may also suppress neurogenic inflammation through elevation of cAMP in sensory neurones. They are, therefore, analgesic, anti-tussive and anti-hyperalgesic in inflammatory diseases associated with irritation and pain.

5

Compounds according to the invention may also elevate cAMP in lymphocytes and thereby suppress unwanted lymphocyte activation in immune-based diseases such as rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease.

10

Compounds according to the invention may also reduce gastric acid secretion and therefore can be used to treat conditions associated with hypersecretion.

15 Compounds of the invention may suppress cytokine synthesis by inflammatory cells in response to immune or infectious stimulation. They are, therefore, useful in the treatment of bacterial, fungal or viral induced sepsis and septic shock in which cytokines such as tumour necrosis factor (TNF) are key mediators. Also compounds of the invention may suppress
20 inflammation and pyrexia due to cytokines and are, therefore, useful in the treatment of inflammation and cytokine-mediated chronic tissue degeneration which occurs in diseases such as rheumatoid or osteo-arthritis.

25 Over-production of cytokines such as TNF in bacterial, fungal or viral infections or in diseases such as cancer, leads to cachexia and muscle wasting. Compounds of the invention may ameliorate these symptoms with a consequent enhancement of quality of life.

30 Compounds of the invention may also elevate cAMP in certain areas of the brain and thereby counteract depression and memory impairment.

Compounds of the invention may suppress cell proliferation in certain tumour cells and can be used, therefore, to prevent tumour growth and
35 invasion of normal tissues.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one
5 or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

10

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or
15 hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for
20 oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous
25 vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

30

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formulae (1) and (2) may be formulated for parenteral
35 administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule

or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents.

- 5 Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

- 10 In addition to the formulations described above, the compounds of formulae (1) and (2) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

- 15 For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

- 20 The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

- 25 The quantity of a compound of the invention required for the prophylaxis or treatment of a particular inflammatory condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or
30 buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

- 35 The compounds according to the invention may be prepared by the following processes. In the reactions described below it may be

necessary to protect reactive functional groups, for example hydroxy, amino, thio, or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T.W. in "Protective Groups in Organic
5 Synthesis" John Wiley and Sons, 1981].

Thus according to a further aspect of the invention a compound of formula (1) may be prepared by reaction of a corresponding intermediate
10 compound of formula (1) wherein R^4 and/or R^5 is a $-(CH_2)_tArNHR^b$ group with an isocyanate $Ar(Alk)_mL^2N=C=O$ or isothiocyanate $Ar(Alk)_mL^2N=C=S$. The reaction may be performed in a solvent, for example an organic solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around $-0^\circ C$ to around ambient temperature.

15 In a variation of this process the starting intermediate amine of formula (1) may first be treated with phosgene in the presence of a base, e.g. an organic amine such as triethylamine, and subsequently reacted with an amine $Ar(Alk)_mL^2NHR^b$ to yield the desired compound of formula (1)
20 wherein R^4 and/or R^5 contains a urea group. The reaction may be carried out in an organic solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at from around $0^\circ C$ to ambient temperature.

The intermediate amines of formula (1) for use as starting materials in
25 these reactions are either described in International Patent Specification Nos. WO94/14742 and WO95/17386 or International patent application No. PCT/GB95/01459, or may be obtained using the processes described therein from known starting materials. The intermediate isocyanates, isothiocyanates and amines also for use in these processes are readily
30 available known compounds or may be prepared from known starting materials using methods analogous to those used for the preparation of the known compounds.

35 N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid,

at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

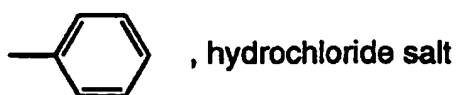
- 5 Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate acid or base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.
- 10 Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.
- 15 Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral acid or base. Suitable chiral acids include, for example, tartaric acid and other tartrates such as dibenzoyl tartrates and ditoluoyl tartrates, sulphonates such as camphor
20 sulphonates, mandelic acid and other mandelates and phosphates such as 1,1'-binaphthalene-2,2'-diyl hydrogen phosphate. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid or base in the instance where the diastereomer is a salt.
25
- In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography.
- Alternatively, a particular enantiomer may be obtained by using an
30 appropriate chiral intermediate in one of the processes described above. Chiral intermediates may be obtained in particular by use of the enantioselective process described in International Patent Specification No. WO95/17386.
- 35 The following Examples illustrate the invention, and describe the preparation of the following compounds:



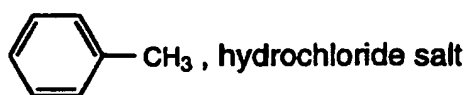
where Cp is cyclopentyl, R⁵ is 4-pyridyl and Ar is:

5

Example 1:

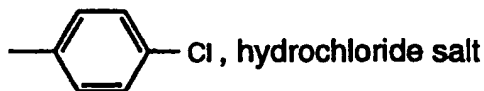


Example 2:



10

Example 3:



15 **EXAMPLE 1**

(R)-N-[4-{1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethyl}-phenyl]-N'-(phenylsulphonyl) urea, hydrochloride

Benzenesulphonylisocyanate (205μl) was added dropwise to a solution of 4-[1-(R)-(3-cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethyl]aniline

20 (500mg prepared as described in International Patent specification No. WO95/17386) in dichloromethane (10ml) under nitrogen at room temperature. The mixture was stirred for 30min at this temperature and the solvent then removed *in vacuo* to yield a yellow gum. Trituration with ether furnished a pale yellow solid (the free base of the title compound

which was dissolved in dichloromethane (5ml) and treated with ethereal HCl to afford a yellow solid. Subsequent recrystallisation of the solid from methanol yielded the title compound (450mg) as an off white solid δ_H (CD₃OD) 1.40-1.90 (8H, br m), 3.64 (2H, d, \downarrow 9Hz), 3.72 (3H, s), 4.34 (1H, t, \downarrow 9Hz), 4.72 (1H, m), 6.75 (3H, d+d+s), 7.20 (4H, d+d), 7.50-7.75 (3H, m), 7.72 (2H, d, \downarrow 8Hz), 8.00 (2H, d, \downarrow 8Hz), and 8.55 (2H, d, \downarrow 8Hz).

The following compounds were prepared in a similar manner to the compound of Example 1:

10

EXAMPLE 2**(R)-N-[4-{1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethyl}-phenyl]-N'-(methylphenylsulphonyl) urea, hydrochloride**

From the starting aniline (1.0g) used in Example 1 and p-toluenesulphonylisocyanate (507mg) in dichloromethane (20ml) at 0-5°C to yield the free base of the title compound (1.29g) as a white solid δ_H (CDCl₃) 1.49-1.95 (8H, m), 2.4 (3H, s), 3.28 (2H, d, \downarrow 7.9Hz), 3.6-3.9 (1H, br s), 3.78 (3H, s), 4.11 (1H, t, \downarrow 6.0Hz), 4.65 (1H, m), 6.62-6.78 (3H, m), 6.95 (2H, d, \downarrow 6.06Hz), 7.1 (2H, d, \downarrow 8.57Hz), 7.26 (4H, m), 7.79 (2H, d, \downarrow 8.37Hz), and 8.40 (3H, m). m/z (ESI) (MH⁺586, 100%).

The solid on treatment with ethereal HCl gave the title compound as an off white solid. (Found: C, 62.04; H, 5.90; N, 6.39. C₃₃H₃₅N₃O₅S. HCl. H₂O requires C, 61.91; H, 5.98, N, 6.56%) δ_H (CD₃OD) 1.45-1.85 (8H, m), 2.38 (3H, s), 3.6 (2H, d, \downarrow 6.0Hz), 3.7 (3H, s), 4.3 (1H, m), 4.68 (1H, br s), 6.68-6.8 (3H, m), 7.1-7.45 (6H, m), 7.7-7.9 (4H, m) and 8.52 (2H, br s).

EXAMPLE 3**(R)-N-[4-{1-(3-Cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethyl}-phenyl]-N'-(4-chlorophenylsulphonyl) urea, hydrochloride**

From the starting aniline (1.0g) used in Example 1 and 4-chlorobenzenesulphonylisocyanate (0.384ml) in dichloromethane (20ml) at 0-5°C to yield the free base of the title compound (1.49g) as a white solid, δ_H (CDCl₃) 1.43-1.9 (8H, m), 3.3 (2H, d, \downarrow 7.82Hz), 3.77 (3H, s), 4.09 (1H, t, \downarrow 7.75Hz, \downarrow 7.96Hz), 4.69 (1H, m), 5.59 (1H, br s), 6.62-6.8 (3H, m),

6.95-7.1 (4H, m), 7.15-7.4 (4H, m), 7.88 (2H, d, \downarrow 7.1Hz), 8.36 (2H, d, \downarrow 6.0Hz) and 8.50 (1H, s); m/z (ESI) (MH^+ 505 100%)

The solid on treatment with ethereal HCl gave the title compound as a light yellow solid (Found: C, 58.33, H, 5.17, N, 6.12. $C_{32}H_{32}ClN_3O_5S \cdot HCl \cdot 0.75H_2O$ requires C, 58.58, H, 5.30, N, 6.41%) δ_H (CD_3OD) 1.42-1.8 (8H, m), 3.12 (2H, d, \downarrow 6.0Hz), 3.68 (3H, s), 4.3 (1H, m), 4.67 (1H, m), 6.72 (3H, m), 7.1-7.25 (4H, m), 7.45-7.55 (2H, m), 7.77 (2H, d, \downarrow 3.0Hz), 7.94 (2H, d, \downarrow 8.7Hz) and 8.55 (2H, d, \downarrow 3.0Hz); m/z (ESI) (MH^+ 606 100%).

10

The advantageous pharmacological properties of the compounds according to the invention may be demonstrated in the following *in vitro* and *in vivo* tests:

15 1. **Isolated Recombinant Human PDE IVA Enzyme**

A gene encoding human PDE IV has been cloned from human monocytes (Livi, *et al.*, 1990, *Molecular and Cellular Biology*, 10, 2678). Using similar procedures we have cloned human PDE IV genes from a number of sources including eosinophils, neutrophils, lymphocytes, monocytes, brain
20 and neuronal tissues. These genes have been transfected into yeast using an inducible vector and various recombinant proteins have been expressed which have the biochemical characteristics of PDE IV (Beavo and Reifsnnyder, 1990, *TIPS*, 11, 150). These recombinant enzymes, particularly the human eosinophil recombinant PDE IVA, have been used
25 as the basis of a screen for potent, selective PDE IV inhibitors.

The enzymes were purified to isoenzyme homogeneity using standard chromatographic techniques.

30 Phosphodiesterase activity was assayed as follows. The reaction was conducted in 150 μ l of standard mixture containing (final concentrations): 50mM 2-[tris(hydroxymethyl)methyl]amino]-1-ethanesulphonic acid (TES) -NaOH buffer (pH 7.5), 10mM $MgCl_2$, 0.1 μ M [3H]-cAMP and vehicle or various concentrations of the test compounds. The reaction was initiated
35 by addition of enzyme and conducted at 30°C for between 5 to 30 min. The reaction was terminated by addition of 50 μ l 2% trifluoroacetic acid

containing [^{14}C]-5'AMP for determining recovery of the product. An aliquot of the sample was then applied to a column of neutral alumina and the [^3H]-cAMP eluted with 10ml 0.1 TES-NaOH buffer (pH8). The [^3H]-5'-AMP product was eluted with 2ml 2M NaOH into a scintillation vial containing
5 10ml of scintillation cocktail. Recovery of [^3H]-5'AMP was determined using the [^{14}C]-5'AMP and all assays were conducted in the linear range of the reaction. Results were expressed as IC_{50} values.

Using this procedure, the compounds according to the invention had IC_{50}
10 values of 4nM (compound of Example 1), 13.9nM (compound of Example 2) and 17.6nM (compound of Example 3).

The compounds of the Examples had little or no activity against other isolated PDE isoenzymes (specifically PDE I, II, III or V - see WO
15 94/14742 for experimental details) at concentrations up to 100 μM , thus illustrating the selectivity of their action against PDE IV.

2. Rat Hepatocyte Metabolism

The improved metabolic stability of the compounds according to the
20 invention was demonstrated in a conventional rat hepatocyte model in which rat hepatocytes were cultured in the presence of test compound. The quantity of compound remaining after a fixed period of time was then determined using mass spectroscopy.

25 Thus in one such test the compound of Example 1 was compared with a related compound particularly described in International Patent Specification No. WO94/14742 in which the phenylsulphonyl group in the compound of Example 1 is replaced by a hydrogen atom. After 3h the percentage of each compound remaining was:

30

Compound of Example 1 - 56%

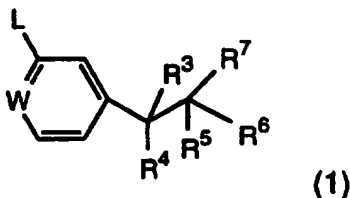
WO 94/14732 comparison compound - 3%.

The WO94/14742 compound had been extensively metabolised whereas
35 over 50% of the compound of the invention remained after 3h, illustrating the advantageous *in vitro* metabolic stability of the compound.

The same two compounds were also administered orally to squirrel monkeys at 10mg/kg p.o., and the plasma levels of each determined. After 1h the WO94/14732 compound was present at 1µg/ml whereas after
5 30min the compound of Example 1 was present at 34µg/ml, thus illustrating the good oral availability of the compound.

CLAIMS

1. A compound of formula (1)



wherein

=W- is (1) =C(Y)- where Y is a halogen atom, or an alkyl or -XR^a group where X is -O-, -S(O)_p- [where p is zero or an integer of value 1 or 2], or -N(R^b)- [where R^b is a hydrogen atom or an optionally substituted alkyl group] and R^a is a hydrogen atom or an optionally substituted alkyl group or, (2) =N-;

L is a -XR, [where R is an optionally substituted alkyl, alkenyl, cycloalkyl or cycloalkenyl group], -C(R¹¹)=C(R¹)(R²) or [-CH(R¹¹)]_nCH(R¹)(R²) group where R¹¹ is a hydrogen or a fluorine atom or a methyl group, and R¹ and R², which may be the same or different, is each a hydrogen or fluorine atom or an optionally substituted alkyl, alkenyl, alkynyl, alkoxy, alkylthio, -CO₂R⁸, [where R⁸ is a hydrogen atom or an optionally substituted alkyl, aralkyl, or aryl group], -CONR⁹R¹⁰ [where R⁹ and R¹⁰, which may be the same or different is each as defined for R⁸], -CSNR⁹R¹⁰, -CN or -NO₂ group, or R¹ and R² together with the C atom to which they are attached are linked to form an optionally substituted cycloalkyl or cycloalkenyl group and n is zero or the integer 1;

R³ is a hydrogen or a fluorine atom, an optionally substituted straight or branched alkyl group, or a hydroxyl group;

R⁴ is a hydrogen atom or group -(CH₂)_tAr [where t is zero or an integer 1, 2 or 3 and Ar is a monocyclic or bicyclic aryl group, optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms] or a group -(CH₂)_t-Ar-(L¹)_n-Ar' [where L¹ is a divalent linking group, n is zero or an integer 1 and Ar' is -Ar, -CO(Alk)_mAr, [where Alk is an optionally substituted straight or branched C₁₋₆ alkylene, C₂₋₆ alkenylene or C₂₋₆ alkynylene chain

- optionally interrupted by one, two or three -O- or -S- atoms or -S(O)_p- (where p is an integer 1 or 2) or -N(R^b)- groups and m is zero or an integer 1], -SO₂(Alk)_nAr, -SO₂NH(Alk)_mAr, -SO₂N(Alk¹)(Alk)_mAr [where Alk¹ is as defined for Alk] -SO₂N[(Alk)_mAr]₂, -CONH(Alk)_mAr,
- 5 -CON(Alk¹)(Alk)_mAr, -CON[(Alk)_mAr]₂, -N(Alk¹)SO₂(Alk)_mAr, -NHSO₂(Alk)_mAr, -N[SO₂(Alk)_mAr]₂, -NHSO₂NH(Alk)_mAr, -N(Alk¹)SO₂NH(Alk)_mAr, -NHSO₂N(Alk¹)(Alk)_mAr, -N(Alk¹)SO₂N(Alk¹)(Alk)_mAr, -NHSO₂N[(Alk)_mAr]₂, -N(Alk¹)SO₂N[(Alk)_mAr]₂, -NHC(O)(Alk)_mAr, -N(Alk¹)C(O)(Alk)_mAr,
- 10 -N[C(O)(Alk)_mAr]₂, -NHC(O)NH(Alk)_mAr, -N(Alk¹)C(O)NH(Alk)_mAr, -NHC(O)N(Alk¹)(Alk)_mAr, -N(Alk¹)C(O)N(Alk¹)(Alk)_mAr, -NHC(O)O(Alk)_mAr, -N(Alk¹)C(O)O(Alk)_mAr, -C(S)NH(Alk)_mAr, -C(S)N(Alk¹)(Alk)_mAr, -C(S)N(Alk¹)(Alk)_mAr, -C(S)N[(Alk)_mAr]₂, -NHC(S)(Alk)_mAr, -N(Alk¹)C(S)(Alk)_mAr, -N[C(S)(Alk)_mAr]₂,
- 15 -NHC(S)NH(Alk)_mAr, -N(Alk¹)C(S)NH(Alk)_mAr, -NHC(S)N(Alk¹)(Alk)_mAr, -N(Alk¹)C(S)N(Alk¹)(Alk)_mAr, -SO₂(Alk)_mNHet
- [where -NHet is an optionally substituted C₅₋₇ heterocyclic amino group optionally containing one or more other -O- or -S- atoms or -N(R^b)-, -C(O)- or -C(S)- groups], -CO(Alk)_mNHet, -CS(Alk)_mNHet,
- 20 -NHSO₂(Alk)_mNHet, -NHC(O)(Alk)_mNHet, -NHC(S)(Alk)_mNHet, -SO₂NH((Alk)_mHet') [where Het' is an optionally substituted C₅₋₇ monocyclic carbocyclic group optionally containing one or more -O- or -S- atoms or -N(R^b)- groups], -CONH((Alk)_mHet'),
- 25 -CSNH((Alk)_mHet'), -NHSO₂NH((Alk)_mHet'), -NHC(O)NH(Alk)_m(Het') or -NHC(S)NH(Alk)_m(Het') group] or R⁴ is a -(CH₂)_tArN(R^b)CX¹N(R^b)L²(Alk)_mAr group where X is an oxygen or sulphur atom and L² is a divalent linking group;
- R⁵ is a -(CH₂)_tAr, -(CH₂)_t-Ar-(L¹)_n-Ar' or
- 30 -(CH₂)_tArN(R^b)CX¹N(R^b)L²(Alk)_mAr group, provided that at least one of R⁴ or R⁵ is a -(CH₂)_tArN(R^b)CX¹N(R^b)L²(Alk)_mAr group;
- R⁶ is a hydrogen or a fluorine atom, or an optionally substituted alkyl group;
- R⁷ is a hydrogen or a fluorine atom, an optionally substituted straight
- 35 or branched alkyl group or an OR^c group where R^c is a hydrogen atom or an optionally substituted alkyl or alkenyl group, or an

alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group; and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

2. A compound according to Claim 1 wherein R^4 is an
5 $-\text{ArN}(\text{R}^b)\text{CXN}(\text{R}^b)\text{L}^2(\text{Ik})_m\text{Ar}$ group.
3. A compound according to Claim 2 wherein L^2 is a $-\text{S}(\text{O})_2$ -or
 $-\text{S}(\text{O})_2\text{NH}-$ group.
- 10 4. A compound according to Claim 3 wherein R^4 is an
 $-\text{ArNHCONHS}(\text{O})_2\text{Ar}$, $-\text{ArNHCSNHS}(\text{O})_2\text{Ar}$,
 $-\text{ArNHCONHS}(\text{O})_2\text{NHA}r$ or $-\text{ArNHCSNHS}(\text{O})_2\text{NHA}r$ group where in
each instance the Ar group is an optionally substituted phenyl group.
- 15 5. A compound according to Claims 1 to 4 wherein $=\text{W}-$ is a $=\text{C}(\text{Y})-$
group and L is a $-\text{XR}$ group.
6. A compound according to Claim 5 wherein Y is an $-\text{OR}^a$ group and
 R^a is an optionally substituted alkyl group
20
7. A compound according to Claim 6 wherein R^a is a methyl group
optionally substituted by one, two or three fluorine or chlorine atoms.
8. A compound according to Claims 1 to 7 wherein L is an $-\text{OR}$ group
25 and R is an optionally substituted cycloalkyl group.
9. A compound according to Claim 8 wherein R is a cyclopentyl group.
10. A compound according to Claims 1 to 9 wherein R^3 , R^6 and R^7 is
30 each a hydrogen atom.
11. A compound according to Claims 1 to 10 wherein R^5 is an Ar group.
12. A compound according to Claim 11 wherein R^5 is an optionally
35 substituted pyridyl group.

13. A compound according to Claim 12 wherein R⁵ is an optionally substituted pyridyl group.

14. A compound which is:

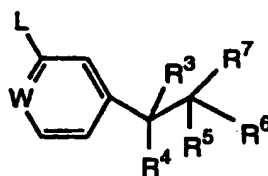
5 (R)-N-[4-{1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethyl}-phenyl]-N'-(phenylsulphonyl) urea;

(R)-N-[4-{1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethyl}-phenyl]-N'-(methylphenylsulphonyl) urea; and

10 (R)-N-[4-{1-(3-cyclopentyloxy-4-methoxyphenyl)-2-(4-pyridyl)ethyl}-phenyl]-N'-(4-chlorophenylsulphonyl) urea;

and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

15 A pharmaceutical composition comprising a compound of formula (1):



(1)

wherein

=W- is (1) =C(Y)- where Y is a halogen atom, or an alkyl or -XR^a group where X is -O-, -S(O)_p- [where p is zero or an integer of value 1 or 2], or -N(R^b)- [where R^b is a hydrogen atom or an optionally substituted alkyl group] and R^a is a hydrogen atom or an optionally substituted alkyl group or, (2) =N-;

L is a -XR, [where R is an optionally substituted alkyl, alkenyl, cycloalkyl or cyloalkenyl group], -C(R¹¹)=C(R¹)(R²) or [-CH(R¹¹)]_nCH(R¹)(R²) group where R¹¹ is a hydrogen or a fluorine atom or a methyl group, and R¹ and R², which may be the same or different, is each a hydrogen or fluorine atom or an optionally substituted alkyl, alkenyl, alkynyl, alkoxy, alkylthio, -CO₂R⁸, [where R⁸ is a hydrogen atom or an optionally substituted alkyl, aralkyl, or aryl group], -CONR⁹R¹⁰ [where R⁹ and R¹⁰, which may be the same or different is each as defined for R⁸], -CSNR⁹R¹⁰, -CN or -NO₂ group, or R¹ and R² together with the C atom to which they are

attached are linked to form an optionally substituted cycloalkyl or cycloalkenyl group and n is zero or the integer 1;

R³ is a hydrogen or a fluorine atom, an optionally substituted straight or branched alkyl group, or a hydroxyl group;

5 R⁴ is a hydrogen atom or group $-(CH_2)_tAr$ [where t is zero or an integer 1, 2 or 3 and Ar is a monocyclic or bicyclic aryl group, optionally containing one or more heteroatoms selected from oxygen, sulphur or nitrogen atoms] or a group $-(CH_2)_tAr-(L^1)_n-Ar'$ [where L¹ is a divalent linking group n is zero or an integer 1 and Ar' is -Ar, -CO(Alk)_mAr, [where Alk is an optionally substituted straight or
10 branched C₁₋₆ alkylene, C₂₋₆ alkenylene or C₂₋₆ alkynylene chain optionally interrupted by one, two or three -O- or -S- atoms or -S(O)_q- (where q is an integer 1 or 2) or -N(R^b)- groups and m is zero or an integer 1], -SO₂(Alk)_nAr, -SO₂NH(Alk)_mAr, -SO₂N(Alk¹)(Alk)_mAr
15 [where Alk¹ is as defined for Alk] -SO₂N[(Alk)_mAr]₂, -CONH(Alk)_mAr, -CON(Alk¹)(Alk)_mAr, -CON[(Alk)_mAr]₂, -N(Alk¹)SO₂(Alk)_mAr, -NHSO₂(Alk)_mAr, -N[SO₂(Alk)_mAr]₂, -NHSO₂NH(Alk)_mAr, -N(Alk¹)SO₂NH(Alk)_mAr, -NHSO₂N(Alk¹)(Alk)_mAr, -N(Alk¹)SO₂N(Alk¹)(Alk)_mAr, -NHSO₂N[(Alk)_mAr]₂,
20 -N(Alk¹)SO₂N[(Alk)_mAr]₂, -NHC(O)(Alk)_mAr, -N(Alk¹)C(O)(Alk)_mAr, -N[C(O)(Alk)_mAr]₂, -NHC(O)NH(Alk)_mAr, -N(Alk¹)C(O)NH(Alk)_mAr, -NHC(O)N(Alk¹)(Alk)_mAr, -N(Alk¹)C(O)N(Alk¹)(Alk)_mAr, -NHC(O)O(Alk)_mAr, -N(Alk¹)C(O)O(Alk)_mAr, -C(S)NH(Alk)_mAr, -C(S)N(Alk¹)(Alk)_mAr, -C(S)N(Alk¹)(Alk)_mAr, -C(S)N[(Alk)_mAr]₂,
25 -NHC(S)(Alk)_mAr, -N(Alk¹)C(S)(Alk)_mAr, -N[C(S)(Alk)_mAr]₂, -NHC(S)NH(Alk)_mAr, -N(Alk¹)C(S)NH(Alk)_mAr, -NHC(S)N(Alk¹)(Alk)_mAr, -N(Alk¹)C(S)N(Alk¹)(Alk)_mAr, -SO₂(Alk)_mNHet

[where -NHet is an optionally substituted C₅₋₇ heterocyclic amino group optionally containing one or more other -O- or -S- atoms or -N(R^b)-, -C(O)- or -C(S)- groups], -CO(Alk)_mNHet, -CS(Alk)_mNHet, -NHSO₂(Alk)_mNHet, -NHC(O)(Alk)_mNHet, -NHC(S)(Alk)_mNHet, -SO₂NH((Alk)_mHet') [where Het' is an optionally substituted C₅₋₇ monocyclic carbocyclic group optionally containing one or more -O- or -S- atoms or -N(R^b)- groups], -CONH((Alk)_mHet'),
35 -CSNH((Alk)_mHet'), -NHSO₂NH((Alk)_mHet'),

-NHC(O)NH(Alk)_m(Het') or -NHC(S)NH(Alk)_m(Het') group] or R⁴ is a -(CH₂)_tArN(R^b)CX¹N(R^b)L²(Alk)_mAr group where X is an oxygen or sulphur atom and L² is a divalent linking group;

R⁵ is a -(CH₂)_tAr, -(CH₂)_t-Ar-(L¹)_n-Ar' or

5 -(CH₂)_tArN(R^b)CX¹N(R^b)L²(Alk)_mAr group, provided that at least one of R⁴ or R⁵ is a -(CH₂)_tArN(R^b)CX¹N(R^b)L²(Alk)_mAr group;

R⁶ is a hydrogen or a fluorine atom, or an optionally substituted alkyl group;

10 R⁷ is a hydrogen or a fluorine atom, an optionally substituted straight or branched alkyl group or an OR^c group where R^c is a hydrogen atom or an optionally substituted alkyl or alkenyl group, or an alkoxyalkyl, alkanoyl, formyl, carboxamido or thiocarboxamido group; and the salts, solvates, hydrates, prodrugs and N-oxides thereof.

15

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 96/03196

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D213/40 A61K31/44 C07D213/64 C07D213/74 C07D213/62
C07D311/60

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 20446 A (CELLTECH LTD) 15 September 1994 see in particular page 11	1-15
X	WO 94 14742 A (CELLTECH LTD) 7 July 1994 cited in the application see in particular page 88	1-15
P,X	WO 95 35281 A (CELLTECH THERAPEUTICS LTD) 28 December 1995 see in particular page 19	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- * "A" document defining the general state of the art which is not considered to be of particular relevance
- * "E" earlier document but published on or after the international filing date
- * "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- * "O" document referring to an oral disclosure, use, exhibition or other means
- * "P" document published prior to the international filing date but later than the priority date claimed

- * "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- * "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- * "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * "&" document member of the same patent family

Date of the actual completion of the international search

27 March 1997

Date of mailing of the international search report

- 9 -06- 1997

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Steendijk, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 96/03196

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9420446 A	15-09-94	AU 675511 B AU 6148994 A EP 0640065 A JP 8505158 T NZ 262170 A	06-02-97 26-09-94 01-03-95 04-06-96 24-02-97
WO 9414742 A	07-07-94	AU 5709294 A CA 2129039 A CN 1092064 A CZ 9402034 A EP 0626939 A FI 943856 A GB 2279075 A,B HU 70559 A HU 9500330 A JP 7504442 T NO 943091 A NZ 258982 A PL 304892 A ZA 9309623 A	19-07-94 07-07-94 14-09-94 15-12-94 07-12-94 22-08-94 21-12-94 30-10-95 30-10-95 18-05-95 21-10-94 24-02-97 09-01-95 18-08-94
WO 9535281 A	28-12-95	AU 2746195 A CA 2192643 A FI 965126 A GB 2302692 A NO 965524 A	15-01-96 28-12-95 19-12-96 29-01-97 20-12-96